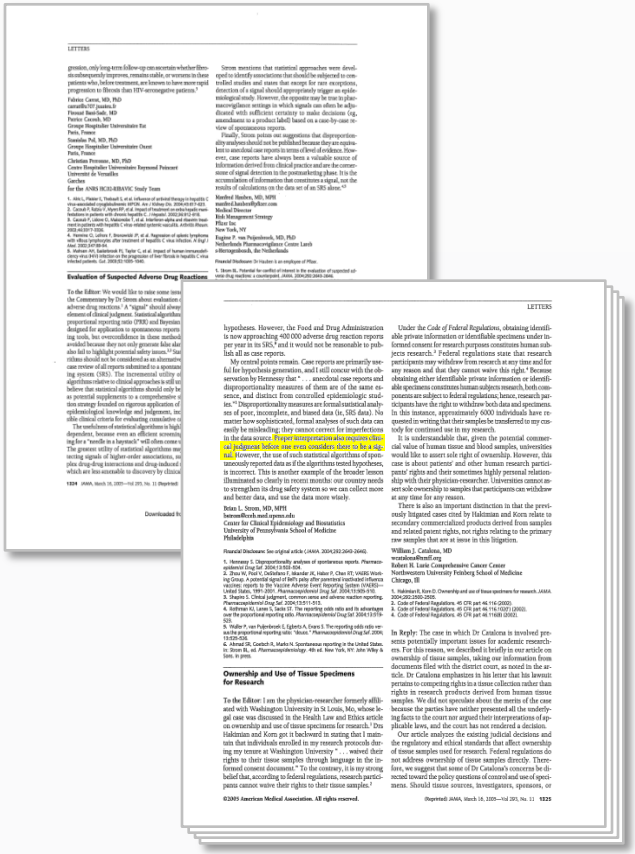
Dr. Ruggieri's Opinions

- Pfizer and Warner-Lambert acted reasonably and complied with regulatory requirements in monitoring the safety of Neurontin
- The information available to Warner-Lambert and Pfizer has consistently failed to support an association or reveal any signal of potential increased risk for depression or suicidal behaviors in patients taking Neurontin
- No signal emerged sufficient to raise special safety concerns in the off-label use of Neurontin
- The Neurontin labeling adequately conveyed necessary information to prescribers regarding the risks and benefits of the medicine

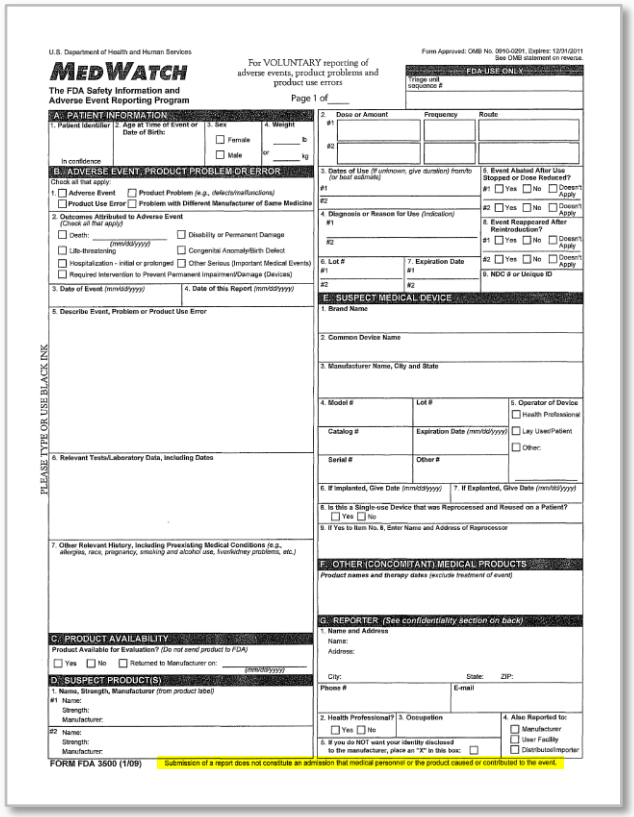
Clinical Judgment Necessary to Interpret Signal



"Proper interpretation also requires clinical judgment before one even considers there to be a signal."

Source: Strom, *JAMA*, 293:1324-5 (2005)

Sample MedWatch Form



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Page 1 of ____

FDA USE ONLY

Triage unit
sequence #

A. PATIENT INFORMATION

1. Patient Identifier / 2. Age at Time of Event or Date of Birth: / 3. Sex: ☐ Female ☐ Male / 4. Weight: _____ lb or _____ kg

In confidence

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: _____ (mm/dd/yyyy) ☐ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy) / 4. Date of this Report (mm/dd/yyyy)

5. Describe Event, Problem or Product Use Error

6. Relevant Tests/Laboratory Data, including Dates

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Name:
Strength:
Manufacturer:
#2 Name:
Strength:
Manufacturer:

2. Dose or Amount / Frequency / Route
#1
#2

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1
#2

4. Diagnosis or Reason for Use (Indication)
#1
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # / 7. Expiration Date
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID
#1
#2

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # / Lot # / 5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other:
Catalog # / Expiration Date (mm/dd/yyyy)
Serial # / Other #
6. If Implanted, Give Date (mm/dd/yyyy) / 7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)

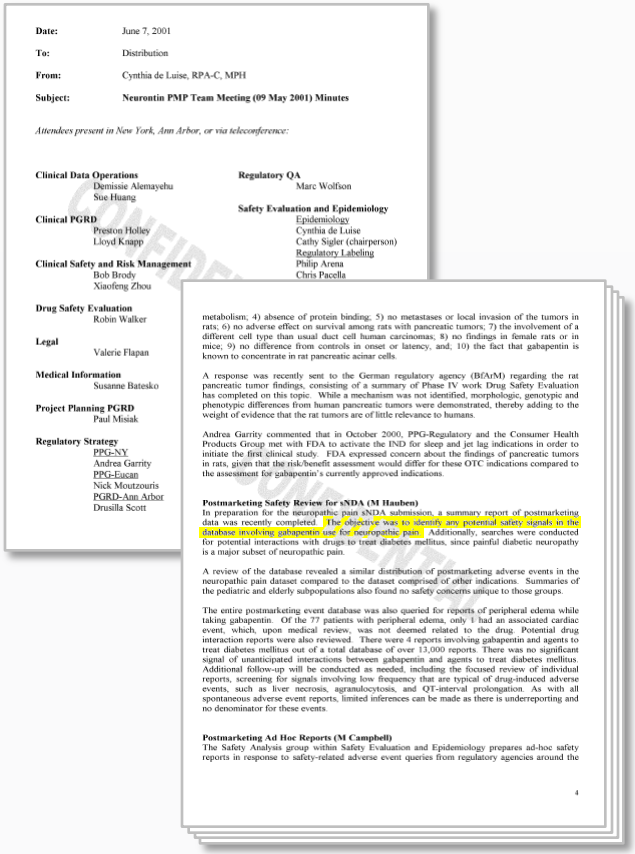
1. Name and Address
Name:
Address:
City: State: ZIP:
Phone # / E-mail
2. Health Professional? ☐ Yes ☐ No / 3. Occupation / 4. Also Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

June 7, 2001 Memo on First Pfizer PMP Meeting



Date: June 7, 2001

To: Distribution

From: Cynthia de Luise, RPA-C, MPH

Subject: **Neurontin PMP Team Meeting (09 May 2001) Minutes**

Attendees present in New York, Ann Arbor, or via teleconference:

Clinical Data Operations
Demissie Alemayehu
Sue Huang

Clinical PGRD
Preston Holley
Lloyd Knapp

Clinical Safety and Risk Management
Bob Brody
Xiaofeng Zhou

Drug Safety Evaluation
Robin Walker

Legal
Valerie Flapan

Medical Information
Susanne Batesko

Project Planning PGRD
Paul Misiak

Regulatory Strategy
PPG-NY
Andrea Garrity
PPG-Eucan
Nick Moutzouris
PGRD-Ann Arbor
Drusilla Scott

Regulatory QA
Marc Wolfson

Safety Evaluation and Epidemiology
Epidemiology
Cynthia de Luise
Cathy Sigler (chairperson)
Regulatory Labeling
Philip Arena
Chris Pacella

metabolism; 4) absence of protein binding; 5) no metastases or local invasion of the tumors in rats; 6) no adverse effect on survival among rats with pancreatic tumors; 7) the involvement of a different cell type than usual duct cell human carcinomas; 8) no findings in female rats or in mice; 9) no difference from controls in onset or latency, and; 10) the fact that gabapentin is known to concentrate in rat pancreatic acinar cells.

A response was recently sent to the German regulatory agency (BfArM) regarding the rat pancreatic tumor findings, consisting of a summary of Phase IV work Drug Safety Evaluation has completed on this topic. While a mechanism was not identified, morphologic, genotypic and phenotypic differences from human pancreatic tumors were demonstrated, thereby adding to the weight of evidence that the rat tumors are of little relevance to humans.

Andrea Garrity commented that in October 2000, PPG-Regulatory and the Consumer Health Products Group met with FDA to activate the IND for sleep and jet lag indications in order to initiate the first clinical study. FDA expressed concern about the findings of pancreatic tumors in rats, given that the risk/benefit assessment would differ for these OTC indications compared to the assessment for gabapentin's currently approved indications.

Postmarketing Safety Review for sNDA (M Hauben)
In preparation for the neuropathic pain sNDA submission, a summary report of postmarketing data was recently completed. The objective was to identify any potential safety signals in the database involving gabapentin use for neuropathic pain. Additionally, searches were conducted for potential interactions with drugs to treat diabetes mellitus, since painful diabetic neuropathy is a major subset of neuropathic pain.

A review of the database revealed a similar distribution of postmarketing adverse events in the neuropathic pain dataset compared to the dataset comprised of other indications. Summaries of the pediatric and elderly subpopulations also found no safety concerns unique to those groups.

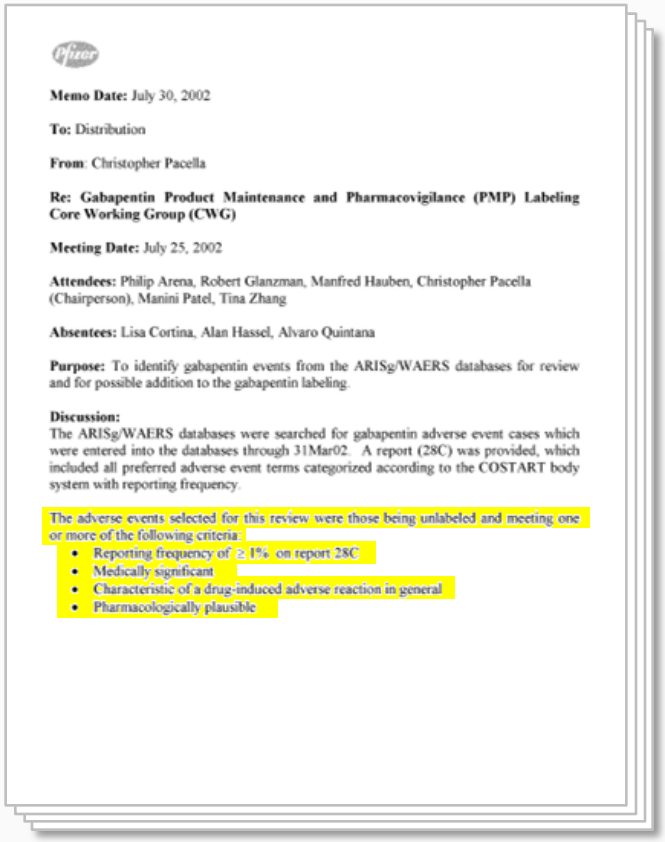
The entire postmarketing event database was also queried for reports of peripheral edema while taking gabapentin. Of the 77 patients with peripheral edema, only 1 had an associated cardiac event, which, upon medical review, was not deemed related to the drug. Potential drug interaction reports were also reviewed. There were 4 reports involving gabapentin and agents to treat diabetes mellitus out of a total database of over 13,000 reports. There was no significant signal of unanticipated interactions between gabapentin and agents to treat diabetes mellitus. Additional follow-up will be conducted as needed, including the focused review of individual reports, screening for signals involving low frequency that are typical of drug-induced adverse events, such as liver necrosis, agranulocytosis, and QT-interval prolongation. As with all spontaneous adverse event reports, limited inferences can be made as there is underreporting and no denominator for these events.

Postmarketing Ad Hoc Reports (M Campbell)
The Safety Analysis group within Safety Evaluation and Epidemiology prepares ad-hoc safety reports in response to safety-related adverse event queries from regulatory agencies around the

4

The objective was to identify any potential safety signals in the database involving gabapentin use for neuropathic pain.

Pfizer Reviewed Adverse Events



Memo Date: July 30, 2002

To: Distribution

From: Christopher Pacella

Re: Gabapentin Product Maintenance and Pharmacovigilance (PMP) Labeling Core Working Group (CWG)

Meeting Date: July 25, 2002

Attendees: Philip Arena, Robert Glanzman, Manfred Hauben, Christopher Pacella (Chairperson), Manini Patel, Tina Zhang

Absentees: Lisa Cortina, Alan Hassel, Alvaro Quintana

Purpose: To identify gabapentin events from the ARISg/WAERS databases for review and for possible addition to the gabapentin labeling.

Discussion:
The ARISg/WAERS databases were searched for gabapentin adverse event cases which were entered into the databases through 31Mar02. A report (28C) was provided, which included all preferred adverse event terms categorized according to the COSTART body system with reporting frequency.

The adverse events selected for this review were those being unlabeled and meeting one or more of the following criteria:

- Reporting frequency of ≥ 1% on report 28C
- Medically significant
- Characteristic of a drug-induced adverse reaction in general
- Pharmacologically plausible

July 25, 2002 Meeting

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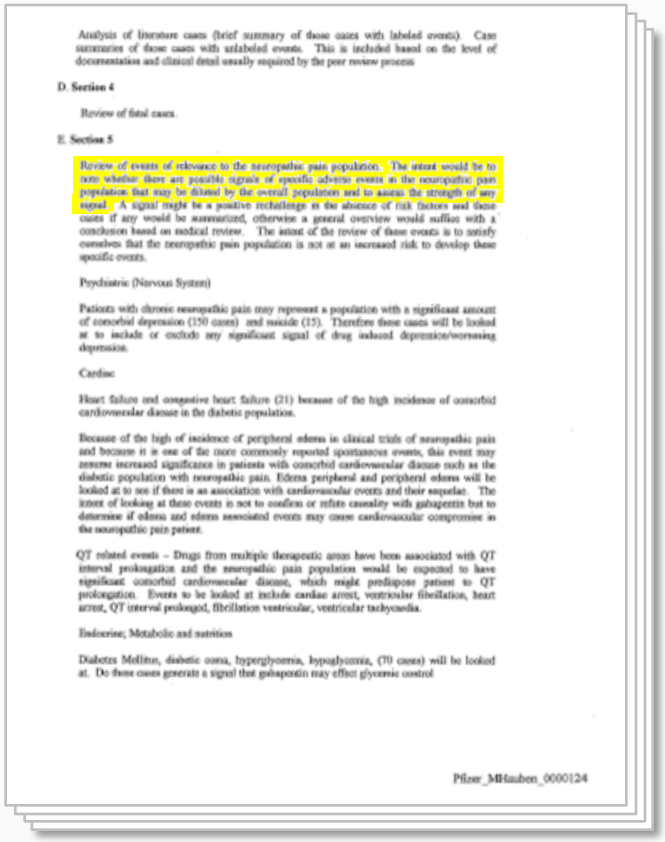
- Characteristics of a drug-induced adverse reaction in general
- Pharmacologically plausible

Pfizer Analyzes Adverse Events in Off-Label Use Populations in 2001



Analysis of literature cases (brief summary of those cases with labeled events). Case summaries of those cases with unlabeled events. This is included based on the level of documentation and clinical detail usually required by the peer review process

D. **Section 4**

Review of fatal cases.

E. **Section 5**

Review of events of relevance to the neuropathic pain population. The intent would be to note whether there are possible signals of specific adverse events in the neuropathic pain population that may be diluted by the overall population and to assess the strength of any signal. A signal might be a positive rechallenge in the absence of risk factors and these cases if any would be summarized, otherwise a general overview would suffice with a conclusion based on medical review. The intent of the review of these events is to satisfy ourselves that the neuropathic pain population is not at an increased risk to develop these specific events.

Psychiatric (Nervous System)

Patients with chronic neuropathic pain may represent a population with a significant amount of comorbid depression (150 cases) and suicide (15). Therefore these cases will be looked at to include or exclude any significant signal of drug induced depression/worsening depression.

Cardiac

Heart failure and congestive heart failure (21) because of the high incidence of comorbid cardiovascular disease in the diabetic population.

Because of the high of incidence of peripheral edema in clinical trials of neuropathic pain and because it is one of the more commonly reported spontaneous events, this event may assume increased significance in patients with comorbid cardiovascular disease such as the diabetic population with neuropathic pain. Edema peripheral and peripheral edema will be looked at to see if there is an association with cardiovascular events and their sequelae. The intent of looking at these events is not to confirm or refute causality with gabapentin but to determine if edema and edema associated events may cause cardiovascular compromise in the neuropathic pain patient.

QT related events – Drugs from multiple therapeutic areas have been associated with QT interval prolongation and the neuropathic pain population would be expected to have significant comorbid cardiovascular disease, which might predispose patient to QT prolongation. Events to be looked at include cardiac arrest, ventricular fibrillation, heart arrest, QT interval prolonged, fibrillation ventricular, ventricular tachycardia.

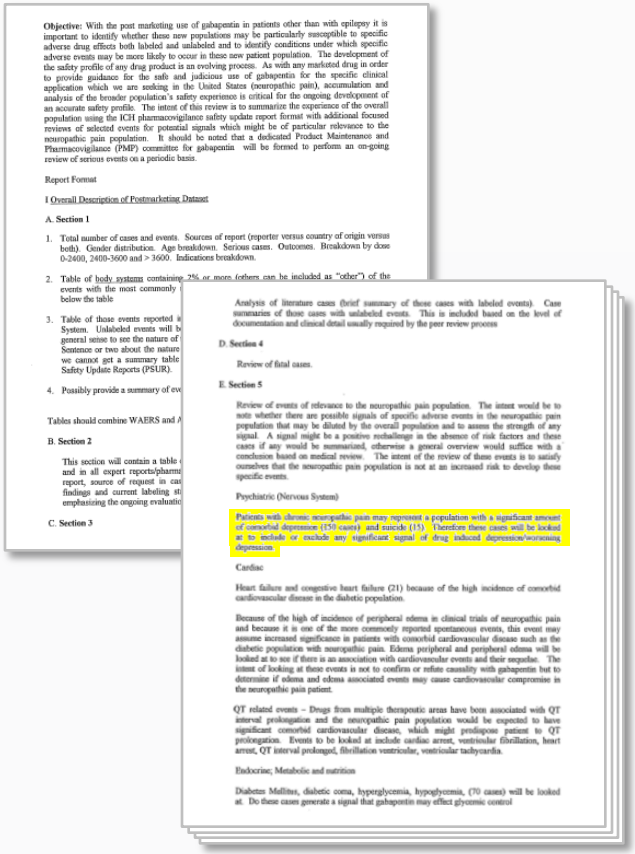
Endocrine; Metabolic and nutrition

Diabetes Mellitus, diabetic coma, hyperglycemia, hypoglycemia, (70 cases) will be looked at. Do these cases generate a signal that gabapentin may effect glycemic control

Pfizer_MBlauben_0000124

Review of events of relevance to the neuropathic pain population. The intent would be to note whether there are possible signals of specific adverse events in the neuropathic pain population that may be diluted by the overall population and to assess the strength of any signal.

Pfizer Analyzes Adverse Events in Neuropathic Pain Population in 2001



Objective: With the post marketing use of gabapentin in patients other than with epilepsy it is important to identify whether these new populations may be particularly susceptible to specific adverse drug effects both labeled and unlabeled and to identify conditions under which specific adverse events may be more likely to occur in these new patient population. The development of the safety profile of any drug product is an evolving process. As with any marketed drug in order to provide guidance for the safe and judicious use of gabapentin for the specific clinical application which we are seeking in the United States (neuropathic pain), accumulation and analysis of the broader population's safety experience is critical for the ongoing development of an accurate safety profile. The intent of this review is to summarize the experience of the overall population using the ICH pharmacovigilance safety update report format with additional focused reviews of selected events for potential signals which might be of particular relevance to the neuropathic pain population. It should be noted that a dedicated Product Maintenance and Pharmacovigilance (PMP) committee for gabapentin will be formed to perform an on-going review of serious events on a periodic basis.

Report Format

I Overall Description of Postmarketing Dataset

A. **Section 1**

1. Total number of cases and events. Sources of report (reporter versus country of origin versus both). Gender distribution. Age breakdown. Serious cases. Outcomes. Breakdown by dose 0-2400, 2400-3600 and > 3600. Indications breakdown.

2. Table of body systems containing 2% or more (others can be included as "other") of the events with the most commonly below the table

3. Table of those events reported System. Unlabeled events will b general sense to see the nature of Sentence or two about the nature we cannot get a summary table Safety Update Reports (PSUR).

4. Possibly provide a summary of ev

Tables should combine WAERS and

B. **Section 2**

This section will contain a table and in all expert reports/pharm report, source of request in ca findings and current labeling e emphasizing the ongoing evaluati

C. **Section 3**

Analysis of literature cases (brief summary of these cases with labeled events). Case summaries of those cases with unlabeled events. This is included based on the level of documentation and clinical detail usually required by the peer review process

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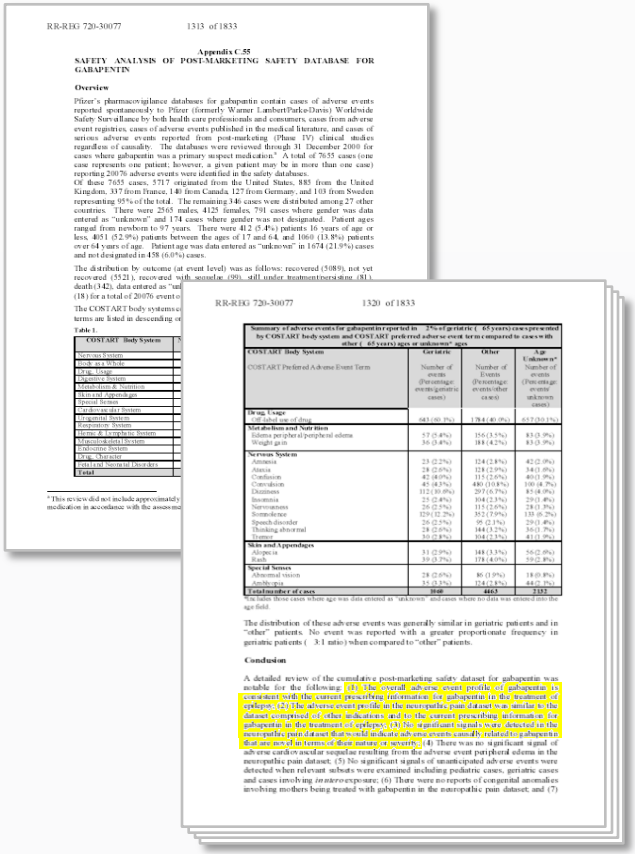
Pfizer's Conclusions on Analysis of Neuropathic Pain Adverse Event Data in 2001



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Appendix C.55

SAFETY ANALYSIS OF POST-MARKETING SAFETY DATABASE FOR GABAPENTIN

Overview

Pfizer's pharmacovigilance databases for gabapentin contain cases of adverse events reported spontaneously to Pfizer (formerly Warner Lambert/Parke-Davis) Worldwide Safety Surveillance by both health care professionals and consumers, cases from adverse event registries, cases of adverse events published in the medical literature, and cases of serious adverse events reported from post-marketing (Phase IV) clinical studies regardless of causality. The databases were reviewed through 31 December 2000 for cases where gabapentin was a primary suspect medication.* A total of 7655 cases (one case represents one patient; however, a given patient may be in more than one case) reporting 20076 adverse events were identified in the safety databases.

Of those 7655 cases, 5717 originated from the United States, 885 from the United Kingdom, 337 from France, 140 from Canada, 127 from Germany, and 103 from Sweden representing 95% of the total. The remaining 346 cases were distributed among 27 other countries. There were 2565 males, 4125 females, 791 cases where gender was data entered as "unknown" and 174 cases where gender was not designated. Patient ages ranged from newborn to 97 years. There were 412 (5.4%) patients 16 years of age or less, 4051 (52.9%) patients between the ages of 17 and 64, and 1060 (13.8%) patients over 64 years of age. Patient age was data entered as "unknown" in 1674 (21.9%) cases and not designated in 458 (6.0%) cases.

The distribution by outcome (at event level) was as follows: recovered (5089), not yet recovered (5521), recovered with sequelae (99), still under treatment/persisting (81), death (342), data entered as "unknown" (1), and not designated (18) for a total of 20076 events.

The COSTART body systems and terms are listed in descending order

Table 1

COSTART Body System
Nervous System
Body as a Whole
Drug Usage
Digestive System
Metabolism & Nutrition
Skin and Appendages
Special Senses
Cardiovascular System
Urogenital System
Respiratory System
Hemic & Lymphatic System
Musculoskeletal System
Endocrine System
Drug Character
Unlisted Neutral Descriptors
Total

*This review did not include approximately medication in accordance with the assessm

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Summary of adverse events for gabapentin reported in 2% of geriatric (65 years) cases presented by COSTART body system and COSTART preferred adverse event term compared to cases with other (65 years) ages or unknown" ages

COSTART Body System COSTART Preferred Adverse Event Term	Geriatric Number of events (Percentage events/geriatric cases)	Other Number of Events (Percentage events/other cases)	Age Unknown* Number of events (Percentage events/ unknown cases)
Drug Usage			
Off label use of drug	683 (40.3%)	1284 (40.0%)	557 (39.1%)
Metabolism and Nutrition			
Edema peripheral peripheral edema	57 (5.4%)	356 (3.5%)	83 (5.9%)
Weight gain	36 (3.4%)	388 (4.2%)	83 (5.9%)
Nervous System			
Amnesia	23 (2.2%)	124 (2.8%)	42 (2.9%)
Ataxia	28 (2.6%)	128 (2.9%)	34 (1.8%)
Confusion	42 (4.0%)	315 (2.6%)	40 (3.9%)
Convulsion	45 (4.3%)	480 (10.8%)	100 (4.3%)
Dizziness	312 (30.0%)	297 (6.7%)	85 (4.0%)
Insomnia	25 (2.4%)	104 (2.3%)	29 (1.4%)
Nervousness	26 (2.5%)	115 (2.6%)	28 (1.3%)
Somnolence	329 (32.2%)	352 (7.9%)	133 (6.2%)
Speech disorder	26 (2.5%)	95 (2.1%)	29 (1.4%)
Thinking abnormal	28 (2.6%)	144 (3.2%)	36 (1.7%)
Tremor	30 (2.8%)	104 (2.3%)	41 (1.9%)
Skin and Appendages			
Alopecia	31 (2.9%)	148 (3.3%)	56 (2.6%)
Rash	39 (3.7%)	178 (4.0%)	59 (2.8%)
Special Senses			
Abnormal vision	28 (2.6%)	86 (1.9%)	18 (0.8%)
Amblyopia	35 (3.3%)	134 (2.8%)	44 (2.1%)
Total number of cases	**1040**	**4463**	**2132**

*Excludes those cases where age was data entered as "unknown" and cases where no data was entered into the age field.

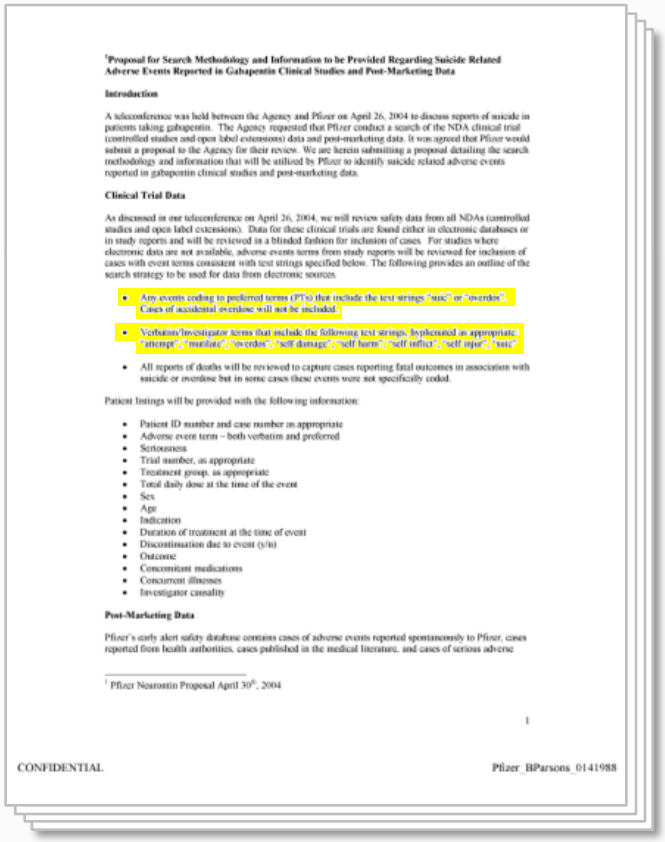
The distribution of these adverse events was generally similar in geriatric patients and in "other" patients. No event was reported with a greater proportionate frequency in geriatric patients (3:1 ratio) when compared to "other" patients.

Conclusion

A detailed review of the cumulative post-marketing safety dataset for gabapentin was notable for the following: (1) The overall adverse event profile of gabapentin is consistent with the current prescribing information for gabapentin in the treatment of epilepsy; (2) The adverse event profile in the neuropathic pain dataset was similar to the dataset comprised of other indications and to the current prescribing information for gabapentin in the treatment of epilepsy; (3) No significant signals were detected in the neuropathic pain dataset that would indicate adverse events causally related to gabapentin that are novel in terms of their nature or severity; (4) There was no significant signal of adverse cardiovascular sequelae resulting from the adverse event peripheral edema in the neuropathic pain dataset; (5) No significant signals of unanticipated adverse events were detected when relevant subsets were examined including pediatric cases, geriatric cases and cases involving *in utero* exposure; (6) There were no reports of congenital anomalies involving mothers being treated with gabapentin in the neuropathic pain dataset; and (7)

1) The overall adverse event profile of [Neurontin] was "consistent with the current prescribing information for [Neurontin] in the treatment of epilepsy;
2) The adverse event profile in the neuropathic pain dataset was similar to the dataset comprised of other indications and to the current prescribing information for [Neurontin] in the treatment of epilepsy; [and]
3) No significant signals were detected in the neuropathic pain dataset that would indicate adverse events causally related to [Neurontin] that are novel in terms of their nature or severity….

FDA Search Strategy Used by Pfizer in 2004 For Suicide Data From 'Electronic Sources'



[1]Proposal for Search Methodology and Information to be Provided Regarding Suicide Related Adverse Events Reported in Gabapentin Clinical Studies and Post-Marketing Data

Introduction

A teleconference was held between the Agency and Pfizer on April 26, 2004 to discuss reports of suicide in patients taking gabapentin. The Agency requested that Pfizer conduct a search of the NDA clinical trial (controlled studies and open label extensions) data and post-marketing data. It was agreed that Pfizer would submit a proposal to the Agency for their review. We are herein submitting a proposal detailing the search methodology and information that will be utilized by Pfizer to identify suicide related adverse events reported in gabapentin clinical studies and post-marketing data.

Clinical Trial Data

As discussed in our teleconference on April 26, 2004, we will review safety data from all NDAs (controlled studies and open label extensions). Data for these clinical trials are found either in electronic databases or in study reports and will be reviewed in a blinded fashion for inclusion of cases. For studies where electronic data are not available, adverse events terms from study reports will be reviewed for inclusion of cases with event terms consistent with text strings specified below. The following provides an outline of the search strategy to be used for data from electronic sources.

- Any events coding to preferred terms (PTs) that include the text strings "suic" or "overdos". Cases of accidental overdose will not be included.
- Verbatim/Investigator terms that include the following text strings, hyphenated as appropriate: "attempt", "mutilate", "overdos", "self damage", "self harm", "self inflict", "self injur", "suic"
- All reports of deaths will be reviewed to capture cases reporting fatal outcomes in association with suicide or overdose but in some cases these events were not specifically coded.

Patient listings will be provided with the following information:

- Patient ID number and case number as appropriate
- Adverse event term – both verbatim and preferred
- Seriousness
- Trial number, as appropriate
- Treatment group, as appropriate
- Total daily dose at the time of the event
- Sex
- Age
- Indication
- Duration of treatment at the time of event
- Discontinuation due to event (y/n)
- Outcome
- Concomitant medications
- Concurrent illnesses
- Investigator causality

Post-Marketing Data

Pfizer's early alert safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported from health authorities, cases published in the medical literature, and cases of serious adverse

[1] Pfizer Neurontin Proposal April 30th, 2004

1

CONFIDENTIAL Pfizer_BParsons_0141988

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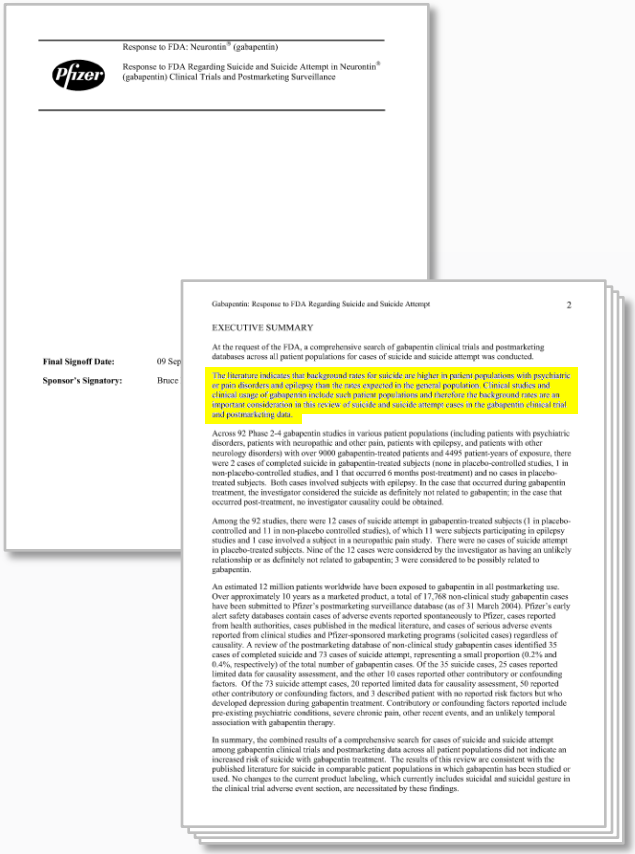
- For studies with no electronic data, adverse event terms from study reports will be reviewed with event terms consistent with certain text strings.

Pfizer 2004 Response to FDA Regarding Suicide and Suicide Attempt in Neurontin – Importance of Background Rates



Response to FDA: Neurontin® (gabapentin)

Response to FDA Regarding Suicide and Suicide Attempt in Neurontin® (gabapentin) Clinical Trials and Postmarketing Surveillance

Final Signoff Date: 09 Sep

Sponsor's Signatory: Bruce

Gabapentin: Response to FDA Regarding Suicide and Suicide Attempt 2

EXECUTIVE SUMMARY

At the request of the FDA, a comprehensive search of gabapentin clinical trials and postmarketing databases across all patient populations for cases of suicide and suicide attempt was conducted.

The literature indicates that background rates for suicide are higher in patient populations with psychiatric or pain disorders and epilepsy than the rates expected in the general population. Clinical studies and clinical usage of gabapentin include such patient populations and therefore the background rates are an important consideration in this review of suicide and suicide attempt cases in the gabapentin clinical trial and postmarketing data.

Across 92 Phase 2-4 gabapentin studies in various patient populations (including patients with psychiatric disorders, patients with neuropathic and other pain, patients with epilepsy, and patients with other neurology disorders) with over 9000 gabapentin-treated patients and 4495 patient-years of exposure, there were 2 cases of completed suicide in gabapentin-treated subjects (none in placebo-controlled studies, 1 in non-placebo-controlled studies, and 1 that occurred 6 months post-treatment) and no cases in placebo-treated subjects. Both cases involved subjects with epilepsy. In the case that occurred during gabapentin treatment, the investigator considered the suicide as definitely not related to gabapentin; in the case that occurred post-treatment, no investigator causality could be obtained.

Among the 92 studies, there were 12 cases of suicide attempt in gabapentin-treated subjects (1 in placebo-controlled and 11 in non-placebo controlled studies), of which 11 were subjects participating in epilepsy studies and 1 case involved a subject in a neuropathic pain study. There were no cases of suicide attempt in placebo-treated subjects. Nine of the 12 cases were considered by the investigator as having an unlikely relationship or as definitely not related to gabapentin; 3 were considered to be possibly related to gabapentin.

An estimated 12 million patients worldwide have been exposed to gabapentin in all postmarketing use. Over approximately 10 years as a marketed product, a total of 17,768 non-clinical study gabapentin cases have been submitted to Pfizer's postmarketing surveillance database (as of 31 March 2004). Pfizer's early alert safety databases contain cases of adverse events reported spontaneously to Pfizer, cases reported from health authorities, cases published in the medical literature, and cases of serious adverse events reported from clinical studies and Pfizer-sponsored marketing programs (solicited cases) regardless of causality. A review of the postmarketing database of non-clinical study gabapentin cases identified 35 cases of completed suicide and 73 cases of suicide attempt, representing a small proportion (0.2% and 0.4%, respectively) of the total number of gabapentin cases. Of the 35 suicide cases, 25 cases reported limited data for causality assessment, and the other 10 cases reported other contributory or confounding factors. Of the 73 suicide attempt cases, 20 reported limited data for causality assessment, 50 reported other contributory or confounding factors, and 3 described patient with no reported risk factors but who developed depression during gabapentin treatment. Contributory or confounding factors reported include pre-existing psychiatric conditions, severe chronic pain, other recent events, and an unlikely temporal association with gabapentin therapy.

In summary, the combined results of a comprehensive search for cases of suicide and suicide attempt among gabapentin clinical trials and postmarketing data across all patient populations did not indicate an increased risk of suicide with gabapentin treatment. The results of this review are consistent with the published literature for suicide in comparable patient populations in which gabapentin has been studied or used. No changes to the current product labeling, which currently includes suicidal and suicidal gesture in the clinical trial adverse event section, are necessitated by these findings.

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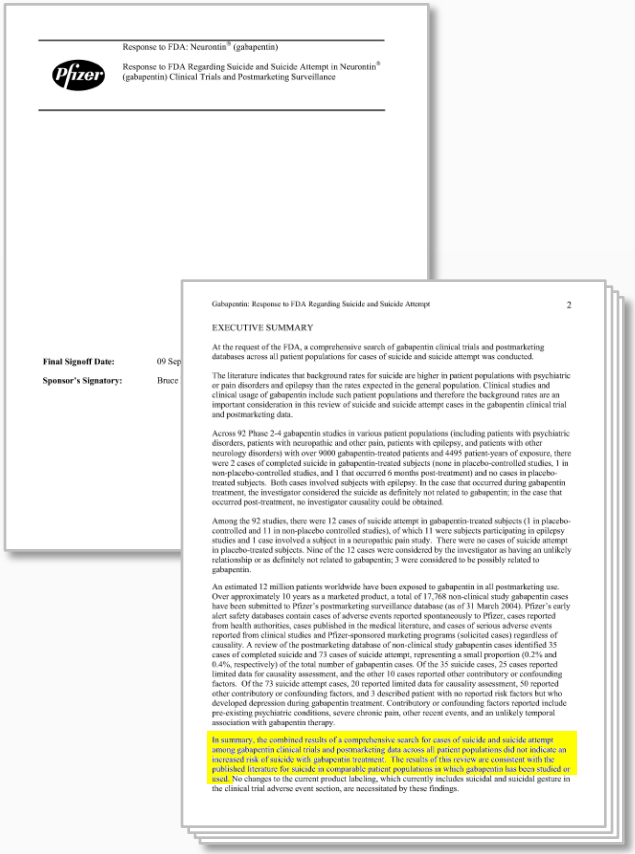
Pfizer 2004 Response to FDA Regarding Suicide and Suicide Attempt in Neurontin – Pfizer's Conclusions



Response to FDA: Neurontin® (gabapentin)

Response to FDA Regarding Suicide and Suicide Attempt in Neurontin® (gabapentin) Clinical Trials and Postmarketing Surveillance

Final Signoff Date: 09 Sep

Sponsor's Signatory: Bruce

Gabapentin: Response to FDA Regarding Suicide and Suicide Attempt 2

EXECUTIVE SUMMARY

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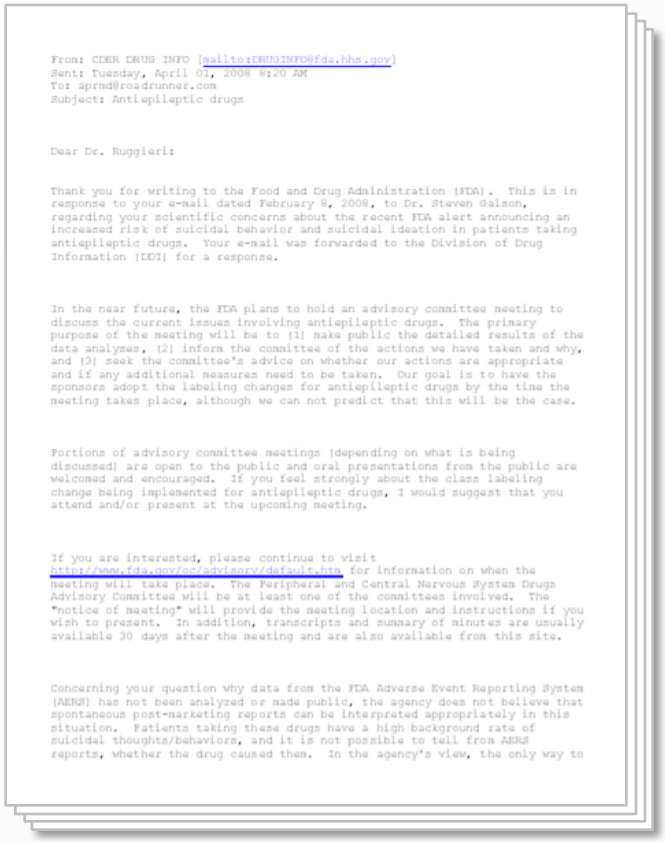
In summary, the combined results of a comprehensive search for cases of suicide and suicide attempt among gabapentin clinical trials and postmarketing data **across all patient populations** did not indicate an increased risk of suicide with gabapentin treatment. The results of this review are consistent with the published literature for suicide in comparable patient populations in which gabapentin has been studied or used.

FDA-Controlled Clinical Trials the Only Way to Establish Whether AEDs Are Responsible for Suicide



From: CDER DRUG INFO [mailto:DRUGINFO@fda.hhs.gov]
Sent: Tuesday, April 01, 2008 9:20 AM
To: aprmd@roadrunner.com
Subject: Antiepileptic drugs

Dear Dr. Ruggieri:

Thank you for writing to the Food and Drug Administration (FDA). This is in response to your e-mail dated February 8, 2008, to Dr. Steven Galson, regarding your scientific concerns about the recent FDA alert announcing an increased risk of suicidal behavior and suicidal ideation in patients taking antiepileptic drugs. Your e-mail was forwarded to the Division of Drug Information (DDI) for a response.

In the near future, the FDA plans to hold an advisory committee meeting to discuss the current issues involving antiepileptic drugs. The primary purpose of the meeting will be to (1) make public the detailed results of the data analyses, (2) inform the committee of the actions we have taken and why, and (3) seek the committee's advice on whether our actions are appropriate and if any additional measures need to be taken. Our goal is to have the sponsors adopt the labeling changes for antiepileptic drugs by the time the meeting takes place, although we can not predict that this will be the case.

Portions of advisory committee meetings (depending on what is being discussed) are open to the public and oral presentations from the public are welcomed and encouraged. If you feel strongly about the class labeling change being implemented for antiepileptic drugs, I would suggest that you attend and/or present at the upcoming meeting.

If you are interested, please continue to visit http://www.fda.gov/cder/advisory/default.htm for information on when the meeting will take place. The Peripheral and Central Nervous System Drugs Advisory Committee will be at least one of the committees involved. The "notice of meeting" will provide the meeting location and instructions if you wish to present. In addition, transcripts and summary of minutes are usually available 30 days after the meeting and are also available from this site.

Concerning your question why data from the FDA Adverse Event Reporting System (AERS) has not been analyzed or made public, the agency does not believe that spontaneous post-marketing reports can be interpreted appropriately in this situation. Patients taking these drugs have a high background rate of suicidal thoughts/behaviors, and it is not possible to tell from AERS reports, whether the drug caused them. In the agency's view, the only way to

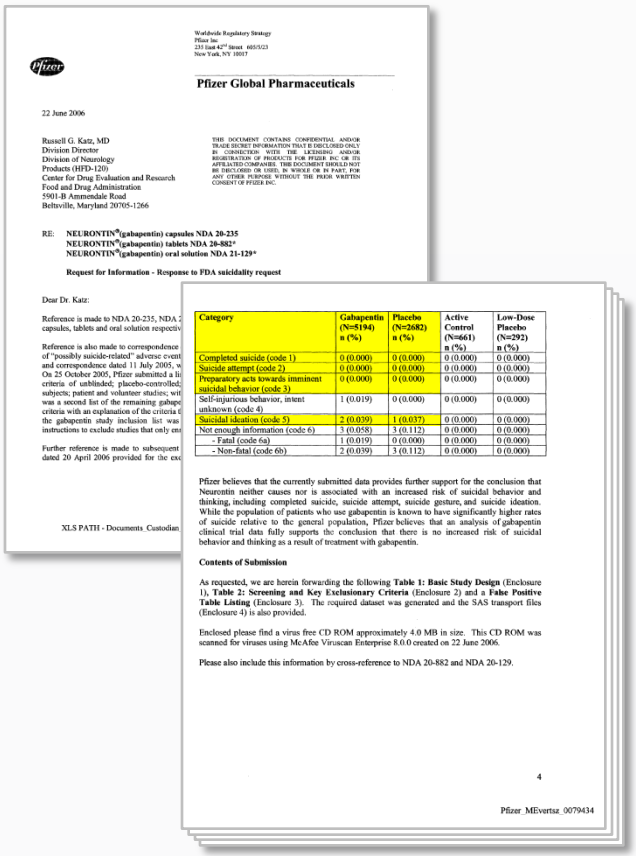
April 1, 2008 E-Mail From FDA to Ruggieri

Patients taking [AEDs] have a high background rate of suicidal thoughts/behaviors, and it is not possible to tell from AERS reports, whether the drug caused them. **In the agency's view, the only way to establish whether or not the drugs are responsible for suicidality is to analyze controlled trial data.**

Source: E-mail from FDA to Dr. Alex Ruggieri (April 1, 2008)

Neurontin Placebo-Controlled Clinical Trial Data

June 22, 2006



Worldwide Regulatory Strategy
Pfizer Inc
235 East 42nd Street 605/5/23
New York, NY 10017

Pfizer Global Pharmaceuticals

22 June 2006

Russell G. Katz, MD
Division Director
Division of Neurology
Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

THIS DOCUMENT CONTAINS CONFIDENTIAL AND/OR TRADE SECRET INFORMATION THAT IS DISCLOSED ONLY IN CONNECTION WITH THE LICENSING AND/OR REGISTRATION OF PRODUCTS FOR PFIZER INC OR ITS AFFILIATED COMPANIES. THIS DOCUMENT SHOULD NOT BE DISCLOSED OR USED, IN WHOLE OR IN PART, FOR ANY OTHER PURPOSE WITHOUT THE PRIOR WRITTEN CONSENT OF PFIZER INC.

RE: **NEURONTIN®(gabapentin) capsules NDA 20-235**
NEURONTIN®(gabapentin) tablets NDA 20-882*
NEURONTIN®(gabapentin) oral solution NDA 21-129*

Request for Information - Response to FDA suicidality request

Dear Dr. Katz:

Reference is made to NDA 20-235, NDA 2
capsules, tablets and oral solution respectiv

Reference is also made to correspondence
of "possibly suicide-related" adverse event
and correspondence dated 11 July 2005, w
On 25 October 2005, Pfizer submitted a li
criteria of unblinded; placebo-controlled;
subjects; patient and volunteer studies; wit
was a second list of the remaining gabape
criteria with an explanation of the criteria f
the gabapentin study inclusion list was
instructions to exclude studies that only en

Further reference is made to subsequent
dated 20 April 2006 provided for the exc

XLS PATH - Documents_Custodian

Category	Gabapentin (N=5194) n (%)	Placebo (N=2682) n (%)	Active Control (N=661) n (%)	Low-Dose Placebo (N=292) n (%)
Completed suicide (code 1)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
Suicide attempt (code 2)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
Preparatory acts towards imminent suicidal behavior (code 3)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
Self-injurious behavior, intent unknown (code 4)	1 (0.019)	0 (0.000)	0 (0.000)	0 (0.000)
Suicidal ideation (code 5)	2 (0.039)	1 (0.037)	0 (0.000)	0 (0.000)
Not enough information (code 6)	3 (0.058)	3 (0.112)	0 (0.000)	0 (0.000)
- Fatal (code 6a)	1 (0.019)	0 (0.000)	0 (0.000)	0 (0.000)
- Non-fatal (code 6b)	2 (0.039)	3 (0.112)	0 (0.000)	0 (0.000)

Pfizer believes that the currently submitted data provides further support for the conclusion that Neurontin neither causes nor is associated with an increased risk of suicidal behavior and thinking, including completed suicide, suicide attempt, suicide gesture, and suicide ideation. While the population of patients who use gabapentin is known to have significantly higher rates of suicide relative to the general population, Pfizer believes that an analysis of gabapentin clinical trial data fully supports the conclusion that there is no increased risk of suicidal behavior and thinking as a result of treatment with gabapentin.

Contents of Submission

As requested, we are herein forwarding the following **Table 1: Basic Study Design** (Enclosure 1), **Table 2: Screening and Key Exclusionary Criteria** (Enclosure 2) and a **False Positive Table Listing** (Enclosure 3). The required dataset was generated and the SAS transport files (Enclosure 4) is also provided.

Enclosed please find a virus free CD ROM approximately 4.0 MB in size. This CD ROM was scanned for viruses using McAfee Viruscan Enterprise 8.0.0 created on 22 June 2006.

Please also include this information by cross-reference to NDA 20-882 and NDA 20-129.

4

Pfizer_MEvertsz_0079434

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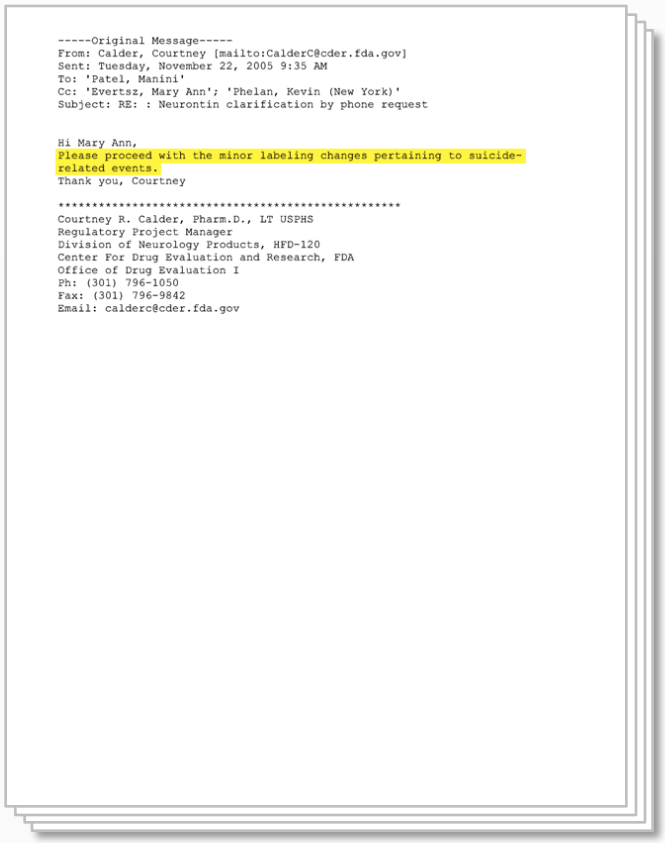
Suicidal ideation (code 5)	2 (0.039)	1 (0.037)
Total	**0.039%**	**0.037%**

Source: Pfizer Submission to FDA at 4 (June 22, 2006); Coronel Decl., Ex. 5

FDA's Minor Labeling Change Request



-----Original Message-----
From: Calder, Courtney [mailto:CalderC@cder.fda.gov]
Sent: Tuesday, November 22, 2005 9:35 AM
To: 'Patel, Manini'
Cc: 'Evertsz, Mary Ann'; 'Phelan, Kevin (New York)'
Subject: RE: : Neurontin clarification by phone request

Hi Mary Ann,
Please proceed with the minor labeling changes pertaining to suicide-related events.
Thank you, Courtney

****
Courtney R. Calder, Pharm.D., LT USPHS
Regulatory Project Manager
Division of Neurology Products, HFD-120
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1050
Fax: (301) 796-9842
Email: calderc@cder.fda.gov

November 22, 2005 E-Mail From FDA to Pfizer

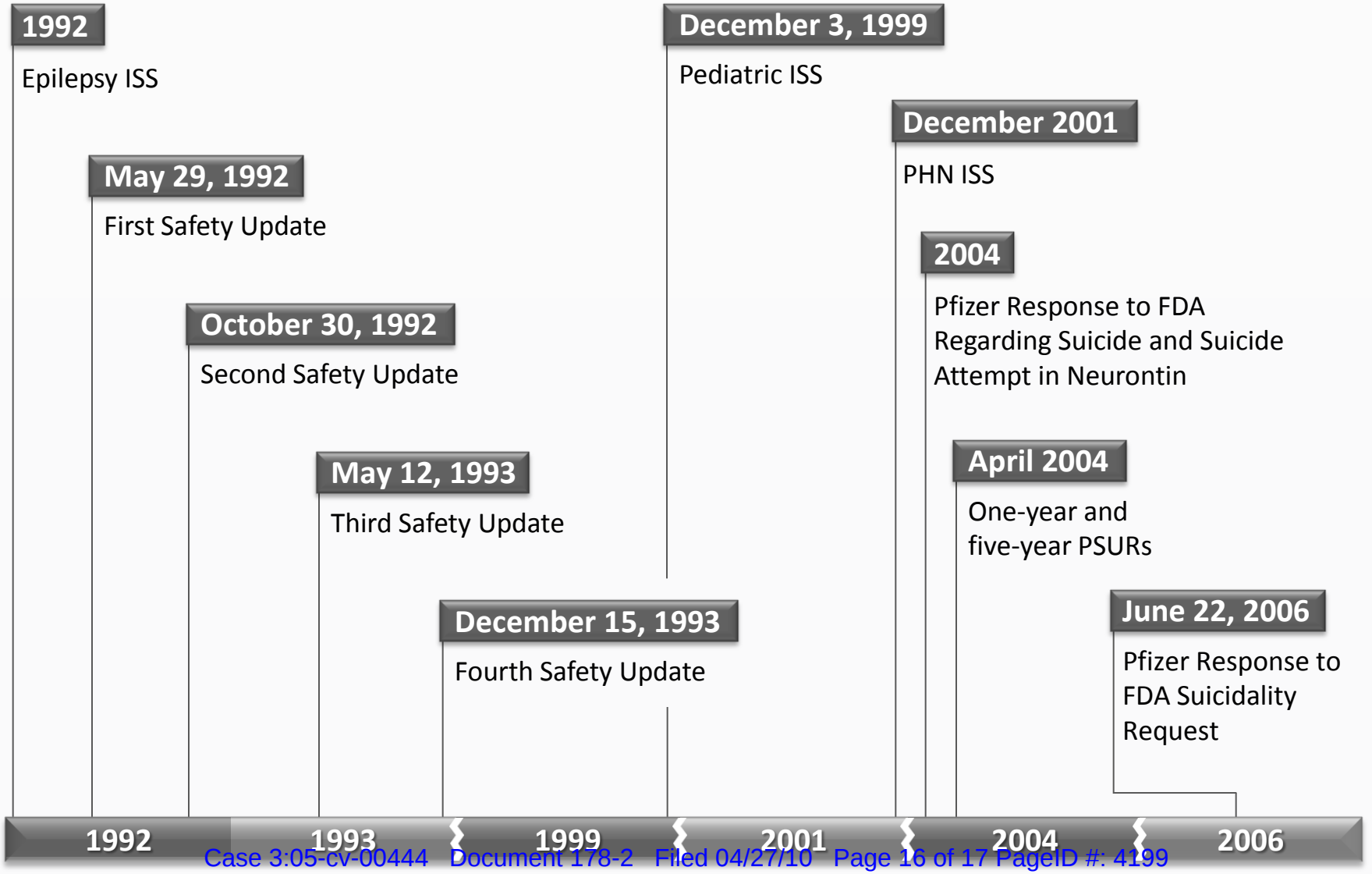
Please proceed with the **minor** labeling changes pertaining to suicide-related events.

Source: E-mail from Courtney Calder to Manini Patel (Nov. 22, 2005)

Top Criticisms of Blume

- The conclusions of the FDA clinical reviewers and the Peripheral and Central Nervous System Advisory Committee indicate that no evidence for an increased risk of suicidality or depression existed based on data from the Neurontin clinical trials in epilepsy.
- FDA's initial labeling decision not to include a warning for suicidal behavior and depression was confirmed repeatedly in subsequent analyses of the Neurontin safety data.
- FDA did not find any individual dechallenge-rechallenge observations sufficient to override the statistically significant comparison of adverse events reported by patients in the treatment and placebo groups.
- Dr. Blume's report repeatedly aggregates or "lumps" multiple adverse events into a category called "Psychobiologic Adverse Events." There is no explanation or medical basis provided in the Blume report of any medical or physiological semantic relationship of this aggregate concept to the concept of suicidality, nor would she by virtue of her qualifications, including her lack of medical training, be able to provide any.
- Dr. Blume's report incorrectly defines the concept of a proportional reporting ratio and subsequently misapplies it in graphical representations. The Blume report also fails to call out the widespread recognition of the limitations of this approach articulated by Dr. Strom as well as by Dr. Greenland.
- Dr. Blume highlights raw numbers of adverse event reports, but she does not calculate rates that provide a measure of risk and are necessary to identify excess risk, nor does she compare rates among comparator groups. She does not compare the rate of suicide in Neurontin patients with those of patients receiving placebo.
- FDA's meta-analysis in 2008 and the subsequent requirement of a class label does not indicate that prior decisions concerning the Neurontin label were wrong. In fact, the Neurontin data analyzed by FDA in 2008 would not suggest the need for a warning.

Safety Data Sent to FDA



Dr. Ruggieri's Opinions

- Pfizer and Warner-Lambert acted reasonably and complied with regulatory requirements in monitoring the safety of Neurontin
- The information available to Warner-Lambert and Pfizer has consistently failed to support an association or reveal any signal of potential increased risk for depression or suicidal behaviors in patients taking Neurontin
- No signal emerged sufficient to raise special safety concerns in the off-label use of Neurontin
- The Neurontin labeling adequately conveyed necessary information to prescribers regarding the risks and benefits of the medicine